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cont*

phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, phosphatidyl
inositol, cardiolipin, sphingomyelin and mixtures thereof.

REMARKS

Claims 25-75 have been cancelled without prejudice and with the right to pursue in subsequent applications.

Applicants have thus added new claims 76-79 which is directed to the species and embodiments within claims 25, 26, 34, 37, 38, 39, 40, 41, 42, 43, and 44 consistent with Applicants' previous election of claims 25-46 and the species C₄F₁₀, air, and phosphatidic acid.

Applicants have also amended the cross referencing information to more accurately reflect the claim to the benefit of the parent applications. A marked up version of the specification is submitted as Exhibit A to show the changes relative to the previous version. No new matter was added.

Pursuant to the duty of candor under 37 C.F.R. § 1.56, Applicants bring to the Examiner's attention the existence of Interference No. 104,427 involving U.S. Pat. No. 5,556,610 to which the subject application is related by way of 35 U.S.C. § 120. The Examiner is requested to examine the interference files when considering this response.

Applicants' previously pending claims have been rejected based on the following grounds:

- a) Claims 25-26, 34, 37, and 41-46 have been rejected under 35 U.S.C. § 112, ¶ 1 based on the species elected (C₄F₁₀, air and phosphatidic acid);
- b) Claims 25-46 have been rejected under 35 U.S.C. § 112, ¶ 2 based on the term "usual";

c) Claims 25-26, 34, 37 and 41-46 have been rejected under the judicially created doctrine of obviousness-type double patenting over a number of commonly owned issued patents and copending applications; and

d) Claims 25-26, 34, 37, 41-42 and 44-46 have been rejected under 35 U.S.C. § 102 (b) over various references: U.S. Pat. 5,205,290 (“Unger ‘290”), U.S. Pat. No. 5,639,443 (“Schutt”), and U.S. Pat. No. 5,562,893 (“Lohrmann”); and

e) Claims 25-26, 34, 37, 41-46 have been rejected under 35 U.S.C. § 103(a) over Schutt in view of U.S. Pat. 5,585,112 (“Unger ‘112”).

Applicants respectfully traverse and will explain below why Applicants’ claims 25-26, 34, 37, and 41-46 are all allowable over the rejections recited. For those same reasons, Applicants’ new claims 76-79 are also allowable. The following remarks, in conjunction with the above amendments, are believed to be fully responsive to the Office Action.

A. Applicants’ Claims Are Patentable Under 35 U.S.C. § 112, ¶ 1

Claims 25-26, 34, 37 and 41-46 have been rejected under 35 U.S.C. § 112, ¶ 1 based on the species elected (*i.e.*, C₄F₁₀, air and phosphatidic acid)

As the Examiner has asserted, the test for compliance with the written description requirement is whether the application reasonably conveys to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully submit that the specification does convey to one skilled in the art that Applicants had possession of the species elected (*i.e.*, C₄F₁₀, air and phosphatidic acid).

For example, the combination of C₄F₁₀ (dodecafluorobutane) and air is specifically disclosed in the specification. *E.g.*, p. 9, lines 25-26. Additionally, one skilled in the art, upon reading the specification’s teaching of dodecafluorobutane as a preferred gas A (p. 9, line 6, p.

12, line 27) and air a preferred gas B (p. 9, line 15), would understand that Applicants had possession of the C₄F₁₀ (dodecafluorobutane) and air gaseous mixture.

Furthermore, phosphatidic acid is specifically disclosed by the Applicants' specification as a preferred film forming surfactant. *E.g.*, p. 13, line 23; p. 15, line 6. Coupled with the disclosure that C₄F₁₀ (dodecafluorobutane) and air are preferred gases, Applicants' specification thus conveys to one skilled in the art that Applicants were in possession of the claimed species invention. Therefore, Applicants' claims satisfy 35 U.S.C. § 112, ¶ 1 and removal of this rejection is respectfully requested. For this same reason, new claims 76-79 also satisfy 35 U.S.C. § 112, ¶ 1.

B. Applicants' Claims Are Patentable Under 35 U.S.C. § 112, ¶ 2

Claims 25-46 were rejected under 35 U.S.C. § 112, ¶ 2 based on the term "usual". Applicants disagree and submit that one of ordinary skill in the art would understand which surfactants, additives and stabilisers may be used since that is conventionally known in the art. However, to expedite prosecution and not for any reasons related to patentability, Applicants have deleted these claims. New claims 75-79 do not contain the term "usual". Thus, this issue is moot and withdrawal of this rejection is respectfully requested.

C. The Claims Are Patentable Under 35 U.S.C. § 102(b)

Claims 25-26, 34, 37 and 41-42 and 44-46¹ have been rejected under 35 U.S.C. § 102 (b) over Unger '290, Schutt, and Lohrmann. Applicants respectfully traverse.

To anticipate a claim, a single prior art reference must disclose each and every element of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477, 44

¹ Of claims 41-42 and 44-46, only claim 41 was rejected over Unger, claims 41-42 were rejected over Schutt, and claims 41-42 and 44-46 were rejected over Lohrmann. They are grouped together for convenience.

U.S.P.Q.2d 1429, 1431 (Fed. Cir. 1997), citing *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 34 U.S.P.Q.2d 1565 (Fed. Cir. 1995); *Verdegall Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1501, 1503 (Fed. Cir. 1987) *cert denied*, 484 U.S. 827 (1987). A prior art reference does not anticipate a claimed invention even if the reference discloses most of or substantially the same elements as the claimed invention. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 756 F.2d 1556, 1560, 225 U.S.P.Q. 253, 256 (Fed.Cir. 1985). Rather, the identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed.Cir. 1989).

Thus, Applicants' claims are patentable over each of the cited references since they each fail to disclose each element of Applicants claims.

1. Unger '290

Unger '290 discloses microspheres made from synthetic polymers or copolymers. Col. 2, lines 30-32. Unger '290 criticized the specific use of lipids since "lipids have a lower electron density than water, lipids provide a negative density on CT (a negative HU value)." Col. 1, lines 49-51. Furthermore, as Unger states, "there is a limitation to the concentration of lipid which a patient can tolerably drink, which puts a limit on the change in density (or HU) which the lipid based CT contrast agent can provide." Col. 1, lines 54-58. Unger also criticizes the use of lipids because "lipid formulations are generally perishable, which provides for packaging and storage problems." Col. 1, lines 59-61. Therefore, Unger's '290 microspheres are limited to vesicles made from synthetic polymers or copolymers.

Furthermore, Unger '290 teaches that its microspheres may have an internal void volume of between 75% to 90% of the total volume of the microsphere. Col. 3, lines 4-10. In that regard, Unger's microspheres are in reality microparticles having different thicknesses.

Contrary to the Examiner's assertion on p. 8 of the Office Action, Unger '290 does not teach anywhere to fill its microspheres with a mixture of two gases. Within a large laundry list of volatile liquids, Unger '290 teaches the use of liquid C₄F₁₀ for its heat expansion process alone, and not in combination with any other gas. Col. 4, lines 9-28. The use of gaseous C₄F₁₀ is never mentioned or even suggested. In fact, the only gases which Unger '290 lists for use in its gas filled microsphere are carbon, dioxide, oxygen, nitrogen, xenon, argon, neon, helium and air. Col. 5, lines 15-17. No gas mixtures are disclosed or envisioned by Unger.

Since Unger '290 fails to teach the use of a gas mixture of C₄F₁₀ and air, Unger '290 cannot anticipate the Applicants' claims. Removal of this rejection is respectfully requested.

For the same reason, Applicants' new claims 76-79 are also allowable over Unger '290.

2. Schutt

The earliest possible effective filing date for Schutt is July 30, 1993, which is later than Applicants' claimed January 24, 1992 filing date of EP 92810046.0 which discloses Applicants' claimed invention through out the specification and claims. (E.g., pp. 7-9, claims 2, 3, 5, 6).

Assuming Schutt is prior art (and Applicants assert that it is not), Schutt discloses a microbubble preparation comprising, *inter alia*, a mixture of a first gas and a second gas. Col. 2, lines 65-67. However, contrary to the Examiner's assertion on p. 9 of the Office Action, Schutt does not disclose anywhere the specific gas mixture of air and C₄F₁₀. The only gas mixtures disclosed by Schutt with C₄F₁₀ are perfluorobutane² (C₄F₁₀) and perfluorohexane (C₆F₁₄) (col. 3, lines 66-67; col. 15, lines 44-46 and 60-61; Example 4) or perfluorobutane (C₄F₁₀) and perfluoropropane (C₅F₁₂) (col. 4, line 3; col. 15, line 61). No other gas mixtures with C₄F₁₀ are disclosed.

² C₄F₁₀ is known as perfluorobutane as well as decafluorobutane.

Therefore, Schutt fails to disclose each element of Applicants' claimed species. Thus, removal of this rejection is respectfully requested.

For the same reason, Applicants' new claims 76-79 are also allowable over Unger.

3. Lohrmann

The earliest possible effective filing date for Lohrmann is June 4, 1993, which is later than Applicants' claimed January 24, 1992 filing date of EP 92810046.0 which discloses Applicants' claimed invention through out the specification and claims. (E.g., pp. 7-9, claims 2, 3, 5, 6).

Assuming Lohrmann is prior art (and Applicants assert that it is not), Lohrmann discloses an oil-in-water emulsion consisting of gas forming chemicals in the liquid state which produce free gas microbubbles when irradiated with ultrasonic energy. Col. 2, lines 26-35. The ultrasonic imaging agent is the emulsion (col. 2, lines 39-40), which remains in the liquid state until it is irradiated with ultrasonic energy, causing free gas microbubbles to be formed and released from the emulsion. Col. 3, lines 32-60. Phospholipids are used as stabilizers in the emulsion to help stabilize the liquid gas forming chemical by causing the temperature at which the liquid gas forming chemical becomes a gas to be raised above its boiling point. Col. 3, lines 49-52. When the free gas microbubbles are released from the emulsion, the phospholipids remain in the emulsion. Therefore, Lohrman does not teach the gas microbubbles of Applicants' claims.

Furthermore, Lohrman does not teach the specific mixture of C₄F₁₀ and air. Decafluorobutane (C₄F₁₀) is disclosed as a liquid gas forming chemical (Table 1), which as discussed above, will then yield free gas microbubbles upon irradiation with ultrasonic energy. For this additional reason, Lohrmann fails to teach each element of Applicants' claims.

Therefore, removal of this rejection is respectfully requested.

For these same reasons, Applicants' new claims 76-79 are also allowable over Unger.

D. Applicants' Claims Are Patentable Under 35 U.S.C. § 103(a)

Claims 25-26, 34, 37, 41-46 have been rejected under 35 U.S.C. § 103(a) over Schutt in view of Unger '112. Applicants respectfully traverse and submit that these pending claims are patentable over the cited references.

Applicants submit that the effective filing date of Unger '112 is November 30, 1993 since it claims the benefit as a continuation in part of over 10 parent applications. As such, Unger '112 is not prior art to the Applicants' claims.

Assuming Unger '112 is prior art (and Applicants assert that it is not), Unger '112 discloses methods for preparing temperature activated gaseous precursor filled liposomes. Col. 4, lines 3-6. These liposomes are bilayer (figure 10) or multi-layered vesicles (figure 9). As the Examiner admits, Unger '112 fails to disclose the use of a gas mixture in his liposomes. Office Action, p. 11.

1. The Mere Fact That References Can Be Modified Or Combined Is Not Enough

As stated by the Court in *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783-1784 (Fed. Cir. 1992)(emphasis added):

The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification.

Thus, the mere fact that references can be combined or modified (and Applicants believe they cannot) does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed.Cir. 1990); MPEP § 2143.01. Hence, the Examiner's attempt to combine the cited references without any overall

suggestion in the references of the desirability of the modification is improper and should be withdrawn.

For example, there is no overall suggestion in the cited combination that a gas mixture is suprior to a single gas as the encapsulated material. There is also no overall suggestion in any of the cited combinations of why the microvesicle at issue should be microbubbles and microballoons as Schutt teaches rather than a bilayer or multi-layer liposome as Unger advocates. There is further no suggestion anywhere of why Applicants' claimed gas mixture of C₄F₁₀ and air should be the encapsulated material instead of any other preferred liquids or gases. In particular, there is no suggestion to ignore Schutts' teaching for using a (C₄F₁₀) and perfluorohexane (C₆F₁₄) mixture or a perfluorobutane (C₄F₁₀) and perfluoropropane (C₅F₁₂) mixture. Since each reference suggests its own desired structure or materials for use, there cannot be any overall suggestion to choose one material and structure over another.

2. **The Modification Cannot Change
The Principle Of Operation Of A Reference**

The proposed modification cannot change the principle of operation of a reference. *In re Ratti*, 123 U.S.P.Q. 349 (C.C.P.A. 1959); MPEP § 2143.01. However, the Examiner's proposed modification would effectively change the principle of operation of each reference. In particular,

- a) Schutt relies on the presence of a first gas (primary modifier gas) and a second gas (gas osmotic agent) that act together to regulate the osmotic pressure within the bubble to maintain its stability within a living being. Col. 8, lines 10-18.
- b) Unger relies on the bilayer or multi layer structure of its liposomes to provide echnogenicity and stability to pressure within the living being. Col. 4, lines 22-24.

Because Schutt relies on the choice of gases to control the osmotic pressure while Unger relies on the liposomal structure for stability, the Examiner's proposed modification would thus

improperly change the principle of operation of these references and withdrawal of this rejection is respectfully requested.

3. **There Is No Reasonable Expectation Of Success**

There also must be a reasonable expectation of success from the prior art in combining the references. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438, 1442 (Fed.Cir. 1991). This motivation to combine and the reasonable expectation of success both must be found in the prior art and not the Applicants' disclosure. *In re Vaeck*, 20 U.S.P.Q.2d at 1442. Using the Applicant's own disclosure in an obviousness analysis is considered improper and prohibited by case law. *Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988)(“Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.”); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988)(“One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.”)

In other words since Unger and Schutt rely on different mechanisms (*i.e.*, choice of gas vs. choice of encapsulating structure) there is no reasonable expectation of success that these references may be combined as suggested by the Examiner.

Without any reasonable expectation of success, it is improper to combine the references cited by the Examiner and withdrawal of this rejection is respectfully requested.

4. **The Cited Combination Still Does Not Yield Applicants' Claimed Invention**

Even if the cited reference combination proposed by the Examiner were somehow proper, no such combination would yield the Applicants' invention.

Contrary to the Examiner's assertion at p. 12 of the Office Action, the use of choice of using C₄F₁₀ and air is not suggested or disclosed anywhere by Schutt or Unger.

Therefore, Applicants' claims are patentable over the cited art and withdrawal of this rejection is respectfully requested.

For these same reasons, Applicants' new claims 76-79 are also allowable over Unger.

E. Double Patenting

Since the pending claims have not yet been patented, Applicants respectfully request that any rejection based on obviousness-type double patenting be held in abeyance until the claims are otherwise indicated to be allowable. Applicants will then offer to file a terminal disclaimer if appropriate.

F. Conclusion

Therefore, as these previously pending claims 25, 26, 34, 37 and 41-46 are fully supported in the specification and are fully patentable over any references cited. For these same reasons, Applicants' new claims 76-79 are allowable and favorable action on these claims is requested.

If, for some reason, Applicants' response do not place the claims in condition for allowance, the Examiner is respectfully asked to contact Applicant's counsel to set up an interview.

No fee is required. If there are additional fees, please charge them to our firm Deposit Account No. 14-1140.

Respectfully submitted,

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MARKED UP VERSION OF SPECIFICATION

(Additions underlined, deletions bracketed)

This application is a divisional [division] of [application] Serial No. 09/021,367 filed February 10, 1998, now U.S. Patent No. 6,183,725, which is a divisional of Serial No. 08/848,912 filed May 1, 1997, now U.S. Patent No. 5,846,518, which is a divisional of Serial No. 08/637,346 filed April 25, 1996, which is a divisional of Serial No. 08/352,108 filed November 30, 1994, now U.S. Patent No. 5,556,610 which claims the benefit of EP 93810885.9, filed December 15, 1993 [which is also a continuation-in-part of serial No. 07/991,237, filed December 16, 1992, now U.S. Patent No. 5,413,774 the entire content of which is hereby incorporated by reference in this application]. This application is also a continuation in part of Serial No. 10/061,299 filed February 4, 2002, which is a continuation of Serial No. 08/855,055 filed May 13, 1997 now abandoned, which is a divisional of Serial No. 08/740,653 filed October 31, 1996, which is a divisional of Serial No. 08/380,588 filed January 30, 1995, now U.S. Patent No. 5,578,292, which is a divisional of Serial No. 07/991,237 filed December 16, 1992, now U.S. Patent No. 5,413,774, which claims the benefit of EP 92810046.0 filed January 24, 1992.

This application is also a continuation in part of Serial No. 09/706,788 filed November 7, 2000, which is a divisional of Serial No. 08/910,152 filed August 13, 1997, now U.S. Patent No. 6,200,548, which is a divisional of Serial No. 08/288,550 filed August 10, 1994, now U.S. Patent No. 5,711,933, which is a divisional of Serial No. 08/033,435 filed March 18, 1993 now abandoned, which is a divisional of Serial No. 07/695,343 filed May 3, 1991 now abandoned, which claims the benefit of EP 90810367.4 filed May 18, 1990. This application is also a continuation in part of Serial No. 10/266,204 filed September 30, 2002, which is a continuation of Serial No. 09/630,537 filed August 1, 2000, now U.S. Patent No. 6,485,705, which is a

divisional of Serial No. 09/021,150 filed February 10, 1998, now U.S. Patent No. 6,136,293,
which is a divisional of Serial No. 08/853,936 filed May 9, 1997, now U.S. Patent No.
6,110,443, which is a divisional of Serial No. 08,456,385 filed June 1, 1995, now U.S.
5,658,551, which is a divisional of Serial No. 08/315,347 filed September 30, 1994 now U.S.
Patent No. 5,531,980 which is a divisional of Serial No. 08,128,540 filed September 29, 1993,
now U.S. Patent No. 5,380,519, which is a divisional of Serial No. 07/775,989 filed November
20, 1991, now U.S. Patent No. 5,271,928, which is the national stage application of
PCT/EP91/00620 filed April 2, 1991 which claims the benefit of EP 90810262.7 filed April 2,
1990. All of these applications are hereby incorporated by reference.